IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
Veronica Mary, et al.

Serial No.: 09/752,926

Filed: 01/02/01

Title: Novel Therapeutic Application of Enoxaparin

Examiner: Leigh Maier

Art Unit: 1623

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APPEAL BRIEF UNDER 37 C.F.R. 1.192

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from the Final Rejection of Claim 1. A copy of this claim is attached hereto as Appendix I.

RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to appellant, appellants' legal representative or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant pending appeal.

STATUS OF THE CLAIMS

Original claims 2-3 were cancelled. Claim 1 remains in the application unamended, and has been finally rejected.

STATUS OF AMENDMENTS

No amendments have been filed subsequent to the final rejection.

SUMMARY OF INVENTION

The invention relates to a new use of Enoxaparin, a low molecular weight heparin - heretofore used primarily for the treatment or prevention of thromboses in the circulatory system – for the treatment of cerebral ischemia.

ISSUES

At issue with respect to the final office action (Paper No. 11) is whether claim 1 is anticipated by Pratt et al. (Haemostasis 1998:28:78-85).

ARGUMENT

The invention claimed in Appellants' finally rejected claim 1 relates specifically to the use of enoxaparin to treat – and reduce the size of – ischemic lesions of cerebral ischemia. By contrast, PRATT et al deal only with the treatment of one of the consequences of cerebral ischemia induced by photothrombotic lesion, namely the edema induced by the ischemia. The reference deals only with the ability of enoxaparin to reduce the edema. It reports a 25-30% reduction in excess water content in the lesion area. However, it is totally silent about any effect on the size of the lesion (ischemia) itself. There is nothing in the reference to hint at, much less suggest or anticipate, applicants' surprising discovery that enoxaparin also has anti-ischemic action and results in a smaller ischemic lesion in treated vs. untreated animals. Accordingly, that anticipation rejection of claim 1 is untenable and should be withdrawn.

It is respectfully submitted that the following arguments convincingly support Appellant's assertions.

SUMMARY

The present application is directed to the use of enoxaparin to treat cerebral ischemia. The action of enoxaparin is linked to a diminution of the cortical lesion and an improvement of the neurologic score of the animals, initialy disturbed by the ischemic process.
By contrast, Pratt et al. (Haemostasis 1998:28: 78-85) investigated the effect of Enoxaparin on Edema following a photothrombic injury in the rat.

The photothrombotic model of cerebral ischaemia in the rat used by Pratt et al (1998) was first developed by Watson et al (1985). Pratt et al demonstrate that enoxaparin can reduce edema in a photothrombotic lesion caused by illuminating the rat cortex with a fiber optic lamp placed in contact with the skull, after administration of a constant dose of the dye, rose bengal. This study did not target any particular vessel, but rather aimed

at causing a focal ischemia within a constant volume of the cerebral cortex, which was then excised and measured for water content. The ischaemic area showed notable edema, which was significantly reduced by post-lesion treatment with enoxaparin. The author does not discuss either the size of the lesion or the neurological deficit provoked by this lesion. This is because the size of the coagulation lesion is predominantly controlled by the size of the beam of light, which causes the activation of the rose bengal dye, which liberates free oxygen radicals and causes blood coagulation. The response to the light is an all or nothing response, as the beam from a fiber optic apparatus has a very precise boundary zone. Indeed, it is rare to find in the prior art articles using the cortical photothrombotic model with assessment of lesion volume. One study by Bailey et al (1995) used this model to assess the neuroprotective activity of isradipine, an L-type calcium channel blocker which had previously been shown to be neuroprotective in a model of middle cerebral artery occlusion (Sauter et al, 1989). However, no reduction in lesion volume was observed in the photothrombotic model. The lack of popularity of the photothrombotic model shows that this model is clearly not adapted to study lesion volume. The model of choice here would be a middle cerebral artery occlusion model. (N.B.: There are a number of methods of occlusion of the middle cerebral artery, including one using rose Bengal to provoke a thrombosis in this artery - which is not the technique practiced by Pratt et al.)

Likewise, the focal photothrombotic model used by Pratt et al. is not suitable for provoking a neurological deficit in the rat. This is because motor coordination in rats is predominantly controlled by sub-cortical structures such as the striatum and basal ganglia (see work by Cabelguen's group, eg Goudard et al, 1992, who ablate the cortex of rats and still provoke coordinated movements).

The photothrombotic lesion does not extend down to the sub-cortical structures (Dietrich et al, 1987 & 1994) and there is therefore no neurological deficit observed. No mention of a neurological deficit has been found in the prior art, which confirms the experimenters observations that, once the anaesthetic effects of the chloral hydrate had worn off, animals had a normal motor behaviour.

Again, the model of choice for a neurological deficit would be a middle cerebral artery occlusion model, where there is an extensive lesion of the striatum.

In conclusion, it is unlikely that enoxaparin was able to affect lesion volume in the photothrombotic rat model and an absence of deficits in motor neuroscore would prevent the detection of benefits in this parameter.

Thus, Examiner's argument that use of enoxaparin for reducing the size the lesion was inherently practiced in the prior art is untenable and unsupported by any basis in fact. In addition, it is submitted that the cited reference does not describe nor suggest the use of enoxaparine in the treatment of cerebral ischemia, wherefore the subject matter of the claim 1 of the present application is not anticipated by the teaching of Pratt et al

In view of the foregoing, the final rejection is untenable and should be overturned. Appellants respectfully request withdrawal of the final rejection and allowance of claim 1.

The Commissioner is hereby authorized to charge these fees and any other fees that are due to this paper to Deposit Account No. 18-1982 for Aventis Pharmaceuticals Inc., Bridgewater, NJ. Please credit any overpayment to Deposit Account No. 18-1982.

Respectfully submitted,

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APPENDIX

I Claim 1

APPENDIX I

Claim 1

1. A method for treating cerebral ischemia comprising administering to a patent in need thereof an effective amount of enoxaparin.